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Pathological response in a triple-negative breast cancer cohort treated with neoadjuvant carboplatin and docetaxel according to Lehmann's refined classification

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Abstract

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Purpose—Triple-negative breast cancer (TNBC) requires the identification of reliable predictors of response to neoadjuvant chemotherapy (NACT). For this purpose, we aimed to evaluate the performance of the TNBCtype-4 classifier in a cohort of TNBC patients treated with neoadjuvant carboplatin and docetaxel (TCb).

Methods—TNBC patients were accrued in a non-randomized trial of neoadjuvant carboplatin AUC 6 and docetaxel 75 mg/m2 for 6 cycles. Response was evaluated in terms of pathological complete response (pCR, ypT0/is ypN0) and residual cancer burden by Symmans et al. Lehmann's subtyping was performed using the TNBCtype online tool from RNAseq data, and germline sequencing of a panel of 7 DNA damage repair genes was conducted.

Results—94 out of the 121 patients enrolled in the trial had RNAseq available. The overall pCR rate was 44.7%. Lehmann subtype distribution was: 34.0% BL1, 20.2% BL2, 23.4% M, 14.9% LAR and 7.4% were classified as ER+. Response to NACT with TCb was significantly associated with Lehmann subtype (p=0.027), even in multivariate analysis including tumor size and nodal involvement, with BL1 patients achieving the highest pCR rate (65.6%), followed by BL2 (47.4%), M (36.4%) and LAR (21.4%). BL1 was associated with a significant younger age at diagnosis and higher ki67 values. Among our 10 germline mutation carriers, 30% were BL1, 40% were BL2 and 30% were M.

Conclusions—TNBCtype-4 is associated with a significantly different pCR rates for the different subtypes, with BL1 and LAR displaying the best and worse responses to NACT respectively.

Keywords

triple negative breast cancer; docetaxel; carboplatin; TNBCtype; Lehmann; BRCA

INTRODUCTION

Triple-negative breast cancer (TNBC), defined by the lack of expression of estrogen receptor (ER), progesterone receptor (PR) and HER-2 overexpression, represents approximately 15% of breast cancers, has no targeted therapies available yet and is associated with an unfavorable prognosis. Many patients with early stage TNBC are now treated with neoadjuvant chemotherapy (NACT), as pre-surgery treatment enables a higher rate of breast conserving surgery, an early exposure of micrometastatic disease to systemic therapy, and, mainly, an in vivo test of the tumor sensitivity to chemotherapy. In addition, it has been consistently shown that pathological response to NACT is strongly correlated with prognosis in TNBC. Patients obtaining a pathological complete response (pCR, defined as non-invasive residual disease in breast and lymph nodes) have a high likelihood of cure, while those with significant residual disease have a dismal prognosis (1,2).

The addition of platinum salts to standard anthracycline-taxane neoadjuvant regimens has demonstrated a significant increase in pCR rates in TNBC, reaching above 50% (3,4), although at the expense of significantly higher toxicity. For instance, the combination of carboplatin and weekly paclitaxel, followed by dose-dense doxorubicin and cyclophosphamide, reached pCR rates of 54% (ypT0/is ypN0) in the CALGB40603 trial, while the combination without carboplatin achieved a pCR rate of 41% (3). In a similar

manner, neoadjuvant treatment with paclitaxel, non-pegylated liposomal doxorubicin and bevacizumab, with or without carboplatin, achieved pCR rates of 53.2% and 36.9%, respectively (p=0.005). In contrast, classical regimens based on anthracyclines and taxanes have shown pCR rates of around 35–40% (5). Neoadjuvant regimens based on taxanes and platinum salts, without anthracyclines, such as the combination of docetaxel and carboplatin, reach pCR rates of around 50% (6,7). However, comparison among different studies could be biased by different patient population and stage of disease.

Nevertheless, about half of the patients will not achieve a pCR, and a significant proportion of these patients will relapse despite NACT. Thus, TNBC requires a reliable predictor of response to NACT that will enable the selection of patients for whom conventional chemotherapy is insufficient, and direct them to clinical trials with new drugs or new therapeutic approaches.

Intrinsic subtype by gene expression profiling provided a new insight into breast cancer, classifying these tumors into 4 subtypes (8,9). Although TNBC and basal-like were initially considered equivalent, TNBC is in fact a highly heterogeneous disease, and only 70–80% of TNBC are classified as PAM50 basal-like subtype (10). Other gene expression-based classifiers of TNBC have arisen in recent years, with some sharing features and subtypes between them, but without complete overlap (11,12). The Lehmann classification (TNBCtype) has become one of the most studied (13). Initially composed of 6 subtypes, further analysis revealed that the mesenchymal stem-like (MSL) and immunomodulatory (IM) subtypes were more a reflection of the tumor microenvironment rather than of the own tumor cells, and, therefore, the classification was simplified into 4 TNBC subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M) and luminal androgen receptor (LAR) (13). A correlation of Lehmann subtypes with pathological response to NACT based on anthracyclines and taxanes was previously observed with the BL1 group having the highest pCR rate (15). The presence of a subset of TNBC tumors that bear features of ER-positive breast cancer has been known for long, with an overexpression of hormone-regulated pathways, and in special androgen signaling (16,17). There is signs of antitumor activity with androgen blockade in patients with expression of androgen receptor in IHC staining and predictive signatures of androgen blockade efficacy are being developed (18,19). In the gene expression level, all new TNBC classifications have identified this LAR subtype, that corresponds with PAM50 non-basal tumors (11–15).

In this study, we aimed to evaluate the predictive value of Lehmann subtyping in a TNBC cohort treated with neoadjuvant carboplatin and docetaxel. In addition, we analyzed its correlation with the PAM50 intrinsic subtype classification.

PATIENTS AND METHODS

Patients and treatment

An ad-hoc study of predictive biomarkers was conducted within a prospective, non-randomized trial evaluating the clinical efficacy of neoadjuvant carboplatin and docetaxel previously published. Patients with newly diagnosed TNBC were accrued from 7 institutions across Spain and Peru. Eligibility criteria included a pathologically confirmed diagnosis of

invasive breast cancer, age over 18, stage I to III disease and no prior chemotherapy treatment for any malignancies. TNBC was defined as the absence of expression of estrogen and progesterone receptor (ER and PR < 1%) and HER2 status was defined as negative using the ASCO/CAP guidelines (20,21). IHC for ER, PR and Ki67 was determined by local review. Patients received six cycles of carboplatin AUC 6 and docetaxel 75 mg/m2 every 3 weeks followed by surgery. G-CSF support was used following individual institution guidelines. Postoperative radiotherapy was indicated following clinical practice guidelines and adjuvant treatment in case of residual disease was left at the physician discretion.

The study was registered at clinicaltrials.gov (NCT 01560663) and was approved by the Ethical Board at all the participating institutions. All patients signed a written informed consent.

Assessment of response

Pathological complete response was defined as the absence of invasive tumor in the breast and axillary lymph nodes (ypT0/is ypN0) and residual disease was assessed by Symmans residual cancer burden calculator (22). Assessment of response was done by local pathology.

Genomic profiling

Extraction of nucleic acids was done centrally at the Translational Oncology Laboratory (LAOT) at the Hospital Gregorio Marañon (Madrid, Spain).

RNA was extracted from formalin fixed paraffin-embedded (FFPE) core biopsies prior to treatment initiation from the breast tumor, using the RNasy FFPE (Quiagen, Germany). RNA quantification and quality control were performed on NanoDrop 2000. Paired samples from non-responders are not available yet.

Intrinsic subtype was performed from PAM110 panels, including the PAM50 gene set, on the nCounter platform (NanoString Technologies Inc, Seattle, USA) at the LAOT facilities. The PAM110 assay included the 50 PAM50 genes plus an additional set aimed to identify the claudin-low signature and neoangiogenesis signatures (see list of genes in Supplementary Table 2). Further details can be found at http://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GPL17071. RNA sequencing (RNAseq) was performed at the University of North Carolina at Chapel Hill (NC, USA). Total FFPE RNA was used to create a total RNAseq library using the Illumina TruSeq Total RNA library Prep Kit with Ribo-Zero Gold Kit. Libraries were then sequenced two per lane on a HiSeq2500 with a 48x7x48 bp configuration. Alignment with the Human Genome Sequence GRCh37 was done using MapSplice v 2.2.1 and RSEM v1.3.0. Analysis of RNAseq data was done in collaboration between the University of North Carolina and the Hospital Gregorio Marañon.

RSEM normalized data was uploaded into the TNBCtype online tool: http://cbc.mc.vanderbilt.edu/tnbc in order to get Lehmann's subtype distribution (23,24). Patients were classified into four subtypes: BL1 (basal-like 1), BL2 (basal-like 2), M (mesenchymal) and LAR (luminal androgen receptor).

In addition, germline DNA from the patients was extracted from whole blood samples prior to the initiation of therapy using the QIAamp the DNA Blood Midi kit (Quiagen, Germany). A panel of 7 DNA damage repair genes (BRCA1, BRCA2, BARD1, PALB2, RAD50, RAD51C and RAD51D) were analyzed through targeted next-generation sequencing, by Sistemas Genómicos (Valencia, Spain).

Statistical analysis

All statistical analyses were performed on R v3.2.1. Fisher's exact test and Chi square test were used for the comparison of categorical variables, Student's t test and Kruskal-Wallis test were used for independent continuous variables, and mutivariate analyses were performed with multiple logistic regressions. Confidence intervals for categorical variables have been estimated with the Clopper-Pearson method.

RESULTS

Patients

From 2010 to 2015, 121 TNBC patients were accrued in seven participating institutions in Spain and Peru. RNAseq could be performed in 97 of the patients included in the cohort (80.2%). In the remaining patients, insufficient amount of RNA extracted from the core biopsies precluded an appropriate analysis. In addition, 2 patients were lost to follow-up with no available information about their outcomes and another patient received only 1 cycle of TCb due to toxicity, and was considered as not evaluable for the analysis. Figure 1.

Baseline characteristics of the patients are summarized in table 1. Median age at diagnosis was 51 years. There were no significant differences between global trial population and patients included in the molecular analysis both in baseline characteristics and response rates (table 1). Almost two thirds of the patients had axillary involvement, 52.1% and 46.8% of the patients had stage II and III disease, respectively. pCR rate among the 94 available patients for molecular analysis was 44.7% and up to 56.4% achieved a pathological good response (pCR or RCBI). Median follow-up was 35 months.

Lehmann subtype distribution

Lehmann subtype distribution was as follows: 34.0% BL1, 20.2% BL2, 23.4% M and 14.9% LAR. Seven patients (7.4%) in our cohort were classified as ER-positive with Lehmann subtyping tool and were discarded for the subtype distribution. Table 2.

In this cohort, 83% were considered Basal-like by PAM50 subtype, approximately two thirds were classified as BL1 and BL2 by TNBCtype-4 (64.1%) and most of the remaining corresponded to M subtype (28.2%). On the contrary, only 6.2% of our non-basal patients by PAM50 were classified as BL1 or BL2, while most of these patients corresponded to LAR (68.8%).

Of the 7 patients considered ER-positive with regards to ESR1 expression, 42.9% were basal-like by PAM50, 42.9% normal-like and 14.3% HER2E.

Baseline characteristics according to Lehmann subtype

We compared baseline characteristics among each of the Lehmann subtypes. Table 3. Except for age and ki67, no significant differences in the clinical-pathological features were found between the 4 subtypes. BL1 and LAR were associated with a significant younger and higher age at diagnosis, respectively (median age 41 and 67.5 years), $p<0.01$. Patients with LAR tumors included in our cohort tended to have more locally advanced tumors than the rest of the subtypes. Indeed, BL1 and LAR tumors had a trend towards a more frequent nodal involvement (78.1% and 85.7% vs 52.6% and 57.1% for BL2 and M, respectively) although these differences did not reach statistical significance ($p=0.18$). Significant differences in ki67 values were observed across subtypes ($p<0.01$), BL1 tumors displayed the highest ki67 values and LAR the lowest. There were no differences in the percentage of high grade tumors (grade 3) nor in tumor size.

Response according to Lehmann subtype

Response to NACT with TCb was significantly associated with Lehmann subtype ($p=0.027$). BL1 patients achieved the highest pCR rate (65.6%, 95% confidence interval (CI) 46.8–81.4%), followed by BL2 (47.4%, 95% CI 24.4–71.1%), M (36.4%, 95% CI 17.2–59.3%) and LAR (21.4%, 4.7–50.8%). Figure 2. Patients classified as ER-positive obtained a pCR rate of 14.3% (95% CI 0.4–57.9%).

When compared to BL1, LAR and M subtypes had significant lower pCR rates, with an OR of achieving a pCR of 0.14 (95% CI 0.32–0.64) and 0.30 (95% CI 0.09–0.95) respectively ($p<0.01$ and $p=0.037$). This significant association was maintained when multivariate analysis including tumor size and nodal involvement were performed for both M and LAR subtypes ($p=0.015$ and $p=0.008$), and BL2 showed a trend towards a worse response too ($p=0.075$).

In accordance with these results, RCB considered as a continuous variable, was significantly different among all four subtypes ($p=0.004$).

Lehmann subtypes among BRCA/non BRCA carriers

Mutational profiling of homologous repair genes was available for 85 of our patients (90.4%). Among our 10 germline mutation carriers (8 in BRCA1, 1 in BRCA2 and 1 in BARD), 30% (n=3) were BL1, 40% (n=4) were BL2 and 30% (n=3) were M. pCR rates among BRCA carriers were similar to those obtained in the general TNBC population (66.6% (n=2) for BL1, 50% (n=2) for BL2 and 33.3% (n=1) for M; $p=1.00$). Supplementary table 1.

DISCUSSION

In this study we evaluated the distribution of TNBCtype-4 subtypes according to the classification of Lehmann et al and its association with response to NACT based on carboplatin and docetaxel (14).

The TNBCtype distribution in our cohort is very similar to the one described by Lehmann et al with their last modified classification (14). BL1 was the most frequent subtype, and the

combination of BL1 and BL2 reached around 50–55% of the samples in both their cohort and ours. Most of the data available on TNBC subtype classification and response to neoadjuvant chemotherapy is based on the former Lehmann's classification into 6 different subtypes (13). For instance, according to the original classification, genomic profiling of 350 TNBC revealed that 15% and 6% were BL1 and BL2, 20% IM, 8% LAR, 17% M and 7% MSL (25). Similar distribution was observed in TNBC included in the GEICAM/2006-03 trial (26). It is worth noting that up to 7% of our TNBC patients were classified as ER+ with regards to ESR1 gene expression, with no specific correlation with PAM50 intrinsic subtype. Prat et al had 17% of their patients classified as ER+, with a similar PAM50 distribution among this group than in our cohort (25).

Regarding the distribution of the TNBCtype in PAM50 basal versus non-basal TNBC, we found a distinct distribution pattern between both groups. PAM50 basal-like were enriched in basal subtypes, whereas LAR was the main component of the non-basal tumors, in accordance to previously described data (25,27).

We found a significant association of the TNBCtype-4 classification with pCR following neoadjuvant carboplatin and docetaxel (p=0.027), with BL1 displaying the highest pCR rates (65.6%). Although differential response with TNBCtype has shown inconsistent results across different cohorts of patients, the benefit in terms of pCR for BL1 has been invariably described (25). It is noteworthy that our BL1 patients exhibited higher pCR rates than those described previously (65.6% vs 40–55% with different combinations) (13,23). BL1, in addition, seems to display the best disease free-survival at 10 years, with a global DFS of 60% (14).

While the TNBCtype classification seems to bring homogeneous data with regards to pCR and long-term outcome for BL1, LAR and BL2 subtypes harbor contradictory data across different studies for long-term survival and pCR rates respectively, although no formal analyses have been conducted. For instance, initial data suggested that BL2 tumors might be a group with a special chemoresistance, as described by Masuda et al, who found no pCR within this group of patients, in a cohort of patients treated with anthracyclines and taxanes (15). However, our BL2 patients achieved a pCR rate of 47.4%, the second highest rate among our cohort. This finding is supported by other studies that found pCR rates among BL2 of around 35–40% (26). As for LAR tumors, while they have been invariably associated with low response rate to NACT, data regarding long-term survival has been contradictory, displaying the best and worst outcome in different studies (14,15,27).

This study may shed some light to the tailoring strategies of neoadjuvant treatments in TNBC, since we could hypothesize that the use of TCb might enable the omission of anthracyclines in specific subsets of TNBC patients. In fact, since BL1 subtype is associated with a significantly younger age at diagnosis and the best pCR rate and 10 year-DFS, this subset of patients could presumably be spared from the anthracycline long-term cardiac toxicity. In addition, the CREATE-X trial recently demonstrated a significant increase in DFS (3y-DFS rate: 69.8% vs 56.1%, HR=0.58, 95% CI 0.39–0.87) and OS (3y-OS rate: 78.8%vs 70.3%, HR=0.52, 95% CI 0.30–0.90) among TNBC with residual disease after NACT who received adjuvant capecitabine (29). We can speculate that capecitabine should

be tested earlier on in association with other drugs in TNBCtype-4 patients not likely to achieve a pCR, such as LAR and M. Thus, performing this classification and tailoring NACT among TNBC patients would definitely improve cost-effectiveness in this setting and optimize treatment, preventing unnecessary toxicities.

On the other hand, LAR tumors have consistently shown low response rates and pCR in other series (30), and, however inconsistent across studies, AR TNBC seem to show a better long-term prognosis, supporting that TNBC/LAR tumors have a distinct biology compared to non-LAR TNBC (15,30–32). AR-driven TNBC represent a subset of tumors for which pCR might not be prognostic, and thus, that may display a favorable outcome despite residual disease after NACT (33,34). This chemoresistance of AR-driven TNBC could be filled by molecularly targeted therapies directed against the androgen receptor (13), which have been evaluated both in the metastatic and early setting (18). For instance, several trials are evaluating adjuvant enzalutamide in TNBC patients with AR+ disease (NCT02750358), as well as in the neoadjuvant setting in combination with chemotherapy (NCT02689427). Although adjuvant antiandrogen therapy in patients with residual disease following NACT seemed like an interesting option to consider, the phase III ENDEAR trial (NCT02929576) was prematurely discontinued.

In addition to the use of the former TNBCtype classification in most of the published data, there is little evidence regarding TNBCtype performance in patients treated with non-anthracycline, platinum salt-containing regimens. Table 4. A recent phase 2 study evaluating the addition of neoadjuvant everolimus to cisplatin and paclitaxel, performed TNBCtype in 48 of their patients, exhibiting similar trends of response to our cohort overall, although it included the MSL subtype (28).

We then analyzed the TNBCtype and PAM50 distribution among carriers of mutation in a panel of 7 homologous repair genes, with all our tumors classified as basal-like by PAM50 and as BL1, BL2 and M with TNBCtype-4. We also analyzed response with regards to mutational status, with no differences in pathological response between carriers and non-carriers. Data regarding TNBCtype distribution among BRCA carriers is still scarce. Isakoff et al described 7 metastatic TNBC with BRCA mutation, and found 42.9% of BL1, 28.6% of M and 14.3% of MSL and unstable respectively (35). Moreover, Telli at al found 9.1% of BL1, 36.4% of IM, 18.2% M, 9.1% MSL and 27.3% of unstable among 11 BRCA1/2 carriers within the PrECOG0105 trial (36). Nevertheless, all these data should be taken with caution due to the small sample size of all three studies.

Our study has some notable strengths. First, it is one of the first cohorts presenting data with the new classification TNBCtype-4. Second, most of the published data comes from retrospective analysis of patients heterogeneously treated, mainly with combinations of anthracyclines and taxanes. Our cohort, in contrast, is uniformly treated with carboplatin and docetaxel, and no data has been published yet about TNBCtype performance in response prediction with this regimen. Third, we present novel data on the subtype distribution and response among BRCA-related genes mutation carriers.

However, our study has some significant limitations, such as the short follow-up available to date, that precludes survival analysis and, mainly, the small sample size and thus, the wide confidence interval ranges obtained.

In conclusion, although confirmation by other independent series is required, Lehmann's refined classification TNBCtype-4 could help select the neoadjuvant therapy in TNBC. Patients with BL subtypes could be candidates for standard chemotherapy, while the remaining subtypes may need to be directed for new, experimental therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

Although gene expression profiling has provided a better understanding of TNBC, there still is a need for the identification of predictors of response to chemotherapy in this subset of patients. Our study brings innovative data on the predictive value of Lehmann's refined classification tool (TNBCtype-4) in a homogeneous cohort of patients treated with a platinum-containing, anthracycline-free, neoadjuvant regimen, carboplatin and docetaxel. This study shows a meaningful differential response to neoadjuvant chemotherapy among the different subtypes, with BL1 and LAR displaying the highest and lowest pCR rates, respectively (65.6% vs 21.4%). This robust association, together with the novel data on the subtype distribution within BRCA-mutated TNBC, provides a new evidence of TNBC heterogeneous biology, which may enable a future selection of therapies in these patients.

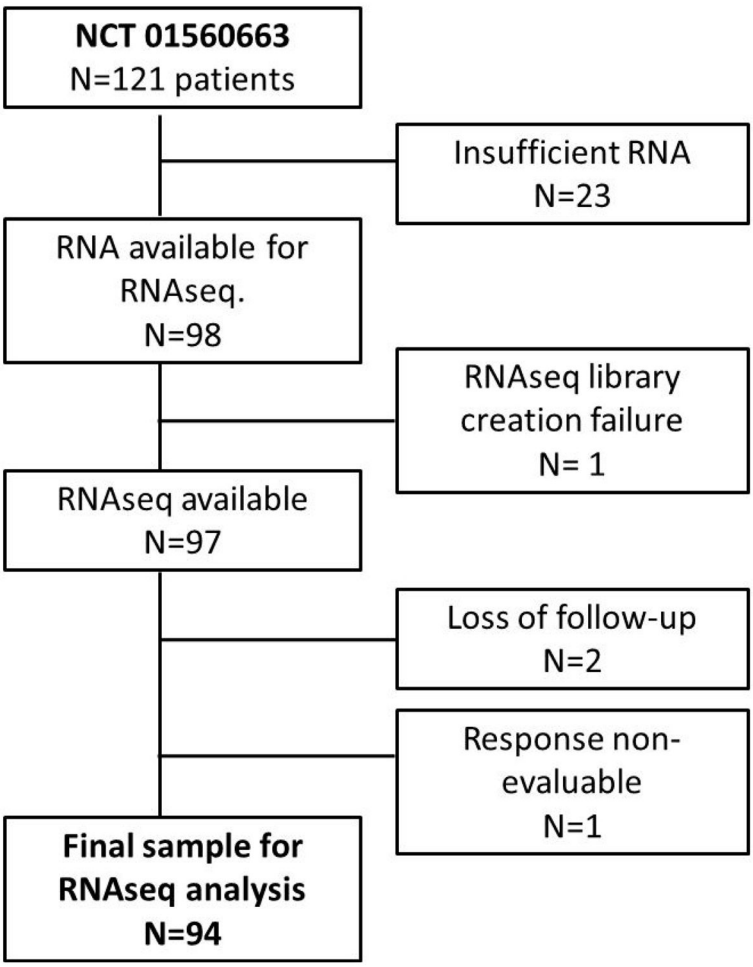

Figure 1.
Consort diagram.

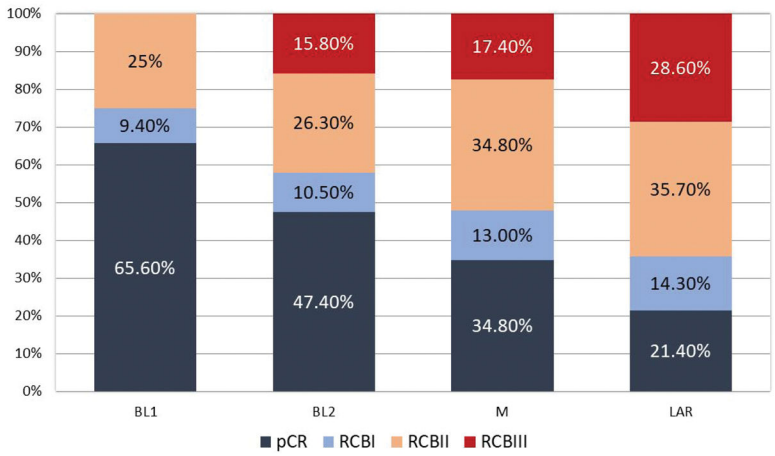

Figure 2. Symmans RCB according to Lehmann subtype

RCB: residual cancer burden. pCR: pathological complete response. BL1: basal-like 1. BL2: basal-like 2. M: mesenchymal. LAR: luminal androgen receptor.

Table 1

Baseline characteristics of our cohort

CI: Confidence interval. MRI: magnetic resonance imaging. N+: node-positive, N0: node-negative. NA: not available. T stage: tumor stage according to AJCC 7th edition. AJCC: American Joint Committee on Cancer. G: grade. Fisher's exact test has been used for categorical variables, Mann Whitney test for comparison of 2 means (age, tumor size and ki67). * Hispanic definition refers to individuals from Latin American ancestry.

	N=121	N=94	p
Age			
Median (range)	51.4 (28–80)	51 (28–78)	0.61
Ethnicity*			
Caucasian	117 (96.7%)	90 (95.7%)	1.0
Asian	2 (1.7%)	2 (2.1%)	
Hispanic	2 (1.7%)	2 (2.1%)	
Menstrual status at diagnosis			
Premenopausal	58 (47.9%)	43 (45.7%)	0.51
Perimenopausal	1 (0.8%)	1 (1.1%)	
Postmenopausal	60 (51.2%)	49 (52.1%)	
NA	2 (1.7%)	1 (1.1%)	
Tumor size by MRI (mm)			
Median, range	40 (9–180)	42 (12–180)	0.65
Axillary involvement			
N0	43 (35.5%)	29 (30.9%)	0.07
N+	78 (64.5%)	65 (69.1%)	
T stage			
T1	4 (3.3%)	4 (4.3%)	0.71
T2	66 (54.5%)	49 (52.1%)	
T3	24 (19.8%)	20 (21.3%)	
T4	27 (22.3%)	21 (22.3%)	
AJCC TNM			
I	1 (0.8%)	1 (1.1%)	0.52
II	66 (54.5%)	49 (52.1%)	
III	54 (44.6%)	44 (46.8%)	
Ki67			
Median, range	70% (3–100%)	70% (3–100%)	0.95
<50%	38 (31.4%)	35 (37.2%)	
Histological grade			
G1–2	31 (25.6%)	22 (23.2%)	0.35
G3	87 (71.9%)	70 (74.5%)	

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	N=121	N=94	p
NA	3 (2.5%)	2 (2.1%)	
Response data			
pCR	57 (47.1%)	42 (44.7%)	0.38
RD	64 (52.9%)	52 (55.3%)	

Table 2

Lehmann subtype distribution according to PAM50 intrinsic subtype

BL1: basal-like 1, BL2: basal-like 2, M: mesenchymal, LAR: luminal androgen receptor, ER+: estrogen-receptor positive. N: number of patients.

		PAM50 intrinsic subtype					
		All		Basal		Non-basal	
		N	%	N	%	N	%
Lehmann TNBC type	BL1	32	34.0%	32	41.0%	0	0%
	BL2	19	20.2%	18	23.1%	1	6.2%
	M	22	23.4%	22	28.2%	0	0%
	LAR	14	14.90%	3	3.8%	11	68.8%
	ER+	7	7.4%	3	3.8%	4	25%

Table 3

Baseline characteristics among Lehmann subtypes

N: number of patients. T size: tumor size, N+: nodal involvement, G3: grade 3. Tests for p-values: Age, T and Ki–Kruskal-Wallis, N and G Fisher's exact test.

	BL1	BL2	M	LAR	P
N	32	19	22	14	
Age median	41	51	50.5	67.5	<0.001
T size (median)	48	40	40	58.5	0.40
N + (%)	78.1%	52.6%	63.6%	85.7%	0.13
Median Ki67	80%	60%	70%	40%	<0.001
G3 (%)	84.4%	63.2%	72.7%	64.3%	0.17

Table 4
pCR rates according to Lehmann TNBCtype-4

Cb: carboplatin. T: docetaxel. CDDP: cisplatin. N: number of patients.

	NCT 01560663	Lehmann 2016(13)	Jovanovic 2017 (24)
N	94	306	48
Treatment	TCb x 6	Anthracyclines and taxanes combinations	CDDP-Paclitaxel +/− Everolimus
TNBCtype-4			
BL1	32 (34.0%)	110 (35.9%)	15 (31%)
BL2	19 (20.2%)	67 (21.9%)	3 (6%)
M	22 (23.4%)	77 (25.2%)	15 (31%)
LAR	14 (14.9%)	52 (17.0%)	4 (8%)
ER+	7 (7.4%)		
MSL			9 (19%)
pCR rates			
BL1	21 (65.6%)	46 (41.8%)	8 (53%)
BL2	9 (47.4%)	12 (17.9%)	1 (33%)
M	8 (36.4%)	29 (37.7%)	7 (47%)
LAR	3 (21.4%)	15 (28.8%)	1 (25%)
ER+	1 (14.3%)	--	--
MSL	--	--	3 (33%)